The opinion in support of the decision being entered today is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
JOHN CLARK and CHRIS DENNING

Appeal 2007-1133
Application 09/593,316
Technology Center 1600

Decided: September 28, 2007

Before DEMETRA J. MILLS, LORA M. GREEN, and NANCY J. LINCK, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-6, 13-16, and 33-37.[1] We have

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[1] Claims 7, 17, 22, and 27-32 are also pending, but stand withdrawn from consideration.

jurisdiction under 35 U.S.C. § 6(b). Claims 1, 3, 4, 6, 13, and 16 are representative of the claims on appeal, and read as follows:

1. Ovine tissue devoid of antibody-detectable Galα(1,3) Gal determinants.

3. Isolated ovine cell or tissue that expresses glycosyl transferase enzymes but does not detectably express α(1,3)galactosyltransferase (α1,3GT).

4. An ovine cell which is heterozygous or homozygous for inactivation of an α1,3GT gene.

6. An ovine animal that is homozygous for inactivation of an α1,3GT gene.

13. A method for producing an ovine that is homozygous for inactivation of an α1,3GT gene, comprising providing an ovine embryo of cells according to claim 4, engrafting the embryo into the uterus of a female, birthing an ovine with an inactivated α1,3GT gene from the engrafted female, and if the birthed ovine has the α1,3GT gene inactivated on only one allele, then mating it with another ovine with an inactivated α1,3GT gene, thereby producing an ovine that is homozygous for inactivation of the α1,3GT gene.

16. A method of xenotransplantation, comprising transplanting tissue devoid of antibody-detectable Galα(1,3) Gal determinants according to claim 1 into a mammal having circulating antibody against Galα(1,3) Gal determinants.

The Examiner relies on the following references:

C. Denning et al., "Deletion of the α(1,3) galactosyl transferase (GGTA1) gene and the prion protein (PrP) gene in sheep," 19 *Nature Biotechnology*, 559-562 (June 2001).

R. Yanagimachi, "Cloning: experience from the mouse and other animals," 187 *Molecular and Cellular Endocrinology*, 241-248 (2002).

Jeffrey L. Platt et al., "Knocking out xenograft rejection," 20(3) *Nature Biotechnology*, 231-232 (March 2002).

Carol J. Phelps et al., "Production of α1,3-Galactosyltransferase-Deficient Pigs," 299 *Science*, 411-413 (January 2003).

Susan M. Rhind et al., "Cloned lambs-lessons from pathology," 21(7) *Nature Biotechnology*, 744 (July 2003).

David N. Wells et al., "Cloning livestock: a return to embryonic cells," *Trends in Biotechnology*, 428-432 (October 2003).

Yoshimi Kuroiwa et al., "Sequential targeting of the genes encoding immunoglobulin – α and prion protein in cattle," 36 *Nature Genetics*, 775-780 (July 2004).

We affirm.

BACKGROUND

According to the Specification, the invention "relates to non-human mammals that are engineered to be deficient in the enzyme α(l,3)galactosyltransferase, and consequently do not express the Galα(l,3)Gal xenoantigen." (*Id.* at 1.)

The Specification teaches that tissue from most mammalian species, when transplanted into humans, undergoes hyperacute rejection as human plasma contains naturally occurring antibodies against carbohydrate determinants of the animal tissue (*id.*).

The main target for the naturally occurring antibodies, as set forth in the Specification, are cell-surface oligosaccharides expressing the determinant Galα(l,3)Gal (*id.* at 2). Humans, apes, and Old World monkeys lack the α-galactosyl epitopes (*id.*), and it has been reported that

approximately 95% of the naturally occurring xenospecific antibodies in human recognize the Galα(l,3)Gal epitope (*id.* at 3).

The Galα(l,3)Gal is made by the enzyme α(l,3)galactosyltransferase (α1,3GT) (*id.* at 2). The Specification teaches that in order for mammals, such as pigs, to become a source of various tissue components, techniques need to be developed to suppress Galα(l,3)Gal expression (*id.* at 3-4). One such way is to disrupt expression of functional α1,3GT expression (*id.* at 5).

Thus, according to the "Summary of the Invention":

> Immunologically compatible animal tissue for xenotransplantation is described in this disclosure. Sequence data for the sheep α(l,3)galactosyltransferase (αl,3GT) gene is provided, which enables construction of targeting vectors for inactivating the αl,3GT gene. Successfully targeted cells can be used as nuclear donors for obtaining animals lacking the Galα (l,3)Gal determinant. The tissues can be transplanted into human patients, without being subject to hyperacute rejection by antibodies to the Galα(l,3)Gal determinant normally present in human serum.

(*Id.* at 6.)

The Specification teaches further:

> For certain aspects of this invention, mammalian cells that have had an α l,3GT gene inactivated artificially in at least one haplotype are used to produce animals that do not express the Galα(l,3)Gal epitope. Nuclear transfer permits a nucleus having an inactivated αl,3GT gene to be transferred from a donor cell or cell line to an embryonic cell or oocyte. An embryo is then formed, engrafted into the uterus of a surrogate host, and used to birth a live neonate. Where the αl,3GT gene is homozygously inactivated, the animal or its progeny are already able to supply cells and tissue lacking the Gala(l,3)Gal epitope. Where the αl,3GT gene is inactivated in only one haplotype, homozygous inactivation can be achieved by standard cross-breeding techniques. Tissue lacking the αl,3GT

> epitope can then be used for transplantation into humans without risk of antigenicity for the natural antibody that is normally the linchpin for hyperacute rejection of xenografts.

(*Id.* at 11-12)

Example 1 of the Specification is drawn to cloning and characterization of ovine α(1,3)galactosyl transferase cDNA (*id.* at 43). Example 2 is drawn to expression and southern blot analysis of the gene (*id.* at 45), and Example 3 is drawn to the construction of targeting vectors from genomic galactosyl transferase DNA (*id.* at 46). Example 4 discusses the disruption of the galactosyl transferase gene by homologous recombination in Black Welsh Moutain fetal fibroblasts (*id.* at 50), while Example 5 discusses targeting of the α1,3GT gene in other breeds, such as the Finn Dorset (*id.* at 52).

Example 6 is drawn to making animals in which the α1,3GT gene is inactivated (*id.* at 53). The Specification notes that:

> Recipients of oocytes with a targeted nucleus, engrafted in the manner outlined, were monitored for the status of their pregnancy by subcu[t]aneous ultrasonic scanning on a weekly basis. Ten recipients were determined to be pregnant 35 days after engraftment. At the time these observations were recorded, insufficient time had passed for any engrafted pregnancies to reach term. Some of the pregnancies were stable, and some started to regress. A fetus and umbilical cord were recovered from one of the regressing pregnancies for analysis.

(*Id.* at 55.)

Analysis of the fetus was consistent with inactivation of the α1,3GT gene on one halotype (*id.*), *i.e.*, the fetus was heterozygous for the gene. According to the Specification, "[f]or animals maintaining their pregnancy,

the progress of the fetus is monitored regularly by ultrasound, and brought to term. Blood cells are collected after birth, to verify that at least one α1,3GT allele has been inactivated." (*Id.*)

DISCUSSION

UTILITY

Claims 5 and 6 stand rejected under 35 U.S.C. § 101 "because the claimed invention is not supported by a substantial utility, a well-established utility, and thus the asserted utility is not credible." (Answer 4.)[2]

The Examiner contends that the "asserted specific utility of the claimed ovine animal is providing ovine cells and tissue suitable for xenotransplantation." (Answer 5.) The question, as the Examiner frames it, "is whether the asserted specific utility is substantial, well established, and credible." (*Id.*) Moreover, the Examiner asserts, it must have a significant and presently available benefit to the public (*id.* at 6).

The Examiner focuses on the fact that the Specification established pregnancy via nuclear transfer cloning using a heterozygous knock-out of the α1,3GT gene, but that each died in utero (*id.*). Thus, the Examiner urges, it is not possible to cross-breed heterozygous sheep to obtain a homozygous knock-out of the α1,3GT (*id.*). The Examiner therefore asserts that "the instantly claimed ovine animal or cells homozygous for α1,3GT inactivation were not materialized at the time of filing, not well established in the art, and

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[2] Claims 5 and 6 were also rejected under 35 U.S.C. § 112, first paragraph, based on the lack of utility under 35 U.S.C. § 101 (Answer 8). To the extent that the rejection of those claims under 35 U.S.C. § 112, first paragraph, depended solely on the utility rejection, the rejection is reversed for the same reasons set forth with respect to the utility rejection.

could not have rendered a significant and presently available benefit to the public, and thus do not impart a substantial utility." (*Id.*)

As to the heterozygous cells, it is the Examiner's position that such cells would still express the Galα(1,3)Gal epitope and thus would not be devoid of antibody-detectable Galα(1,3)Gal determinants (*id.*). In addition, the Examiner asserts, citing Phelps and Kuroiwa, while it may be possible to use the heterozygous cells as a starting point in homologous recombination in culture to achieve homozygous inactivation, "although theoretically possible, has proven to be extremely difficult to achieve in the pertinent art, and at the time of the instant filing it has yet to become a reality for any species of *farm* animals." (*Id.* at 7.)

The Examiner bears the initial burden of showing that a claimed invention lacks patentable utility. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). ("Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility.").

The Court of Appeals for the Federal Circuit addressed the utility requirement in *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005). The *Fisher* court interpreted *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966), as rejecting a "de minimis view of utility." 421 F.3d at 1370, 76 USPQ2d at 1229. The *Fisher* court held that § 101 requires a utility that is both substantial and specific. *Id.* at 1371, 76 USPQ2d at 1229. The court held that disclosing a substantial utility means "show[ing] that an invention is useful to the public as disclosed in its current form, not that it

may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that that claimed invention has a significant and presently available benefit to the public." *Id.*, 76 USPQ2d at 1230.

The court held that a specific utility is "a use which is not so vague as to be meaningless." *Id.* In other words, "in addition to providing a 'substantial' utility, an asserted use must show that that the claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.*

We agree with Appellants that the Examiner has not provided a sufficient basis to challenge the Specification's assertion of utility, and the rejection is reversed.

Appellants argue that "ovine tissue devoid of antibody-detectable Galα(1,3)Gal determinants are useful and under development in a number of laboratories for use in xenotransplantation (Br.[3] 25). We do not find "that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness." *Brana*, 51 F.3d at 1566, 34 USPQ2d at 1441. Generating an ovine that is homozygous for inactivation of the α1,3GT gene "does not suggest an inherently unbelievable undertaking or involve implausible scientific principles." (*Id.*)

Several references of record discuss the generation of gene targeted sheep. For Example, McCreath et al. ("Production of gene-targeted sheep by nuclear transfer from cultured somatic cells," 405 *Nature*, 1066-1069 (July 2000)) discuss gene targeting in fetal fibroblasts and the production of

[3] All references to the Brief (Br.) are to the Amended Appeal Brief dated May 9, 2006.

live sheep from fetal fibroblasts. Similarly, Scnieke et al. ("Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts," 278 *Science* 2130-2133 (December 1997)) discloses the production of a transgenic sheep expressing a neomycin resistant marker by nuclear transfer. Campbell (US Patent No. 6,147,276, issued November 14, 2000) and Campbell (US Patent No. 6,252,133 B1, issued June 26, 2001) each teach the generation of transgenic animals using nuclear transfer techniques. Further, Seidman (US Patent No. 5,589,369, issued December 31, 1996) teaches a method of producing homozygotic cells employing homologous recombination.

As to use of an animal that is homozygous for inactivation of an α1,3GT gene, d'Apice (US Patent No. 5,849,991, issued December 15, 1998) teaches that non-viable, non-antigenic xenografts are commonly used in vascular reconstruction (bovine arteries) and in cardiac surgery (porcine cardiac valves) (col. 1, ll. 62-64). In addition, according to d'Apice, elimination or reduction of α(1,3)galactosyltransferase activity in animals used as sources for xenografts would reduce the hyperacute rejection of such xenografts (*see, e.g.*, col. 2, ll. 39-55; col. 6, ll.12-23).

The cited references demonstrate that one of skill in the art would not find the invention of claim 5 and 6 to be incredible. Thus, the fact situation in this Appeal is distinguishable from that in *Fisher*. In *Fisher*, the court found that none of the uses asserted by the applicant in that case were either substantial or specific. The uses were not substantial because "all of Fisher's asserted uses represent merely hypothetical possibilities, objectives which the claimed ESTs, or any EST for that matter, *could* possibly achieve, but none for which they have been used in the real world." *Fisher*, 421 F3d

at 1373, 76 USPQ2d at 1231. "Consequently, because Fisher failed to prove that its claimed ESTs can be successfully used in the seven ways disclosed in the '643 application, we have no choice but to conclude that the claimed ESTs do not have a 'substantial' utility under § 101." *Id.* at 1374, 76 USPQ2d at 1232. In the instant case, if the an ovine of animal that is homozygous for inactivation of an α1,3GT gene were to produced, it would have the real world, substantial use in xenotransplantation as discussed in the d'Apice reference, and such a use would also be specific.

We do, however, agree with Appellants (Br. 24) the arguments made under this statutory basis are essentially enablement rejections.

ENABLEMENT

Claims 1-6, 13-16, and 33-37 stand rejected under 35 U.S.C. § 112, first paragraph, "as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."[4] (Answer 8.) To the extent that the claims are not argued separately, we focus our analysis on claim 6.

Enablement is a question of law, based on underlying findings of fact. *See, e.g., In re Wands*, 858 F.2d 731, 735, 8 USPQ2d 1400, 1402

[4] The Examiner makes separate findings as to the enablement of claim 16, but as we conclude that the Specification is not enabling for making the material of claim 1 required in the xenotransplantation method of claim 16, we find the separate findings as to claim 16 to be moot, and we do not address them here.

(Fed. Cir. 1988). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright*, 999 F.2d at 1561, 27 USPQ2d at 1513 (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23, 20 USPQ2d 1438, 1445 & n. 23 (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1372, 52 USPQ2d 1129, 1138 (Fed. Cir. 1999). Whether the amount of experimentation required is "undue" is determined by reference to the well-known *Wands* factors. *See Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.[5]

"Patent protection is granted in return for an enabling disclosure . . . , not for vague intimations of general ideas that may or may not be workable."

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[5] The factual considerations discussed in *Wands* are: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Genentech, 108 F.3d at 1366, 42 USPQ2d at 1005. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, *reasonable detail* must be provided in order to enable members of the public [skilled in the art] to understand and carry out the invention." *Id.* at 1366, 42 USPQ2d at 1005 (emphasis added).

The Examiner made the following findings with respect to the following factors set out in *Wands*.

The amount of direction or guidance presented and the existence of working examples:

The Examiner notes that the claimed somatic cells that are homozygous for inactivation of an α1,3GT gene are not exemplified by the Specification, and neither are animals homozygous for inactivation of the α1,3GT gene, nor tissues and organs devoid of Galα(1,3) Gal determinants (Answer 9).

According to the Examiner,

> In the specification, the appellant provides an ovine embryo of cells heterozygous for inactivation of an αl,3GT gene, reduces to engraft the embryo into a uterus of a sheep host. However, at the time of the effective filing date, none of the lambs comprising the *heterologous* inactivation of al,3GT gene were born alive. In fact, each died in utero. Thus, the αl,3GT+/- lamb, the starting material for crossbreeding, is missing, one cannot mate a heterozygous fetus to obtain a sheep devoid of Galα(1,3)Gal determinants. In view of the disclosure, the enablement of instantly claimed invention very much depends on the state of the prior art.

(*Id.* at 10-11.)

In regard to the disclosed method of targeting a cell that is heterozygous for the α1,3GT gene with an inactivation vector to inactivate the α1,3GT gene on the other haplotype, the Examiner notes that the "[S]pecification fails to actually provide such [a] cell at the time of instant filing." (*Id.* at 13.)

Nature of the invention and the state of the prior art:

The invention is drawn to the production of an ovine animal that is homozygous for inactivation of the α1,3GT gene (*see, e.g.*, Answer 10).

According to the Examiner, the art of somatic nuclear transfer (NT) cloning at the time the application was filed was underdeveloped and many barriers hampered the success of the method (*id.* at 11). The Examiner asserts that the "general state of the art was such that somatic NT cloning in farm animals was and still is highly inefficient, and the underlying mechanism for such inefficiency had not been fully understood, which reflects the under-developed state of the art, and such inefficiency cannot be resolved by routine experimentation." (*Id.*)

The Examiner cites Denning, a post-filing date publication, for its teaching of the difficulties of somatic cell targeting (*id.*). Specifically, Denning is cited for its teaching that "[a] substantial number of colonies with only targeted cells senesced before they could be prepared for nuclear transfer. The high attrition rate of targeted clonal populations suitable for nuclear transfer represents one of the major hurdles of gene targeting in primary somatic cells." (Answer 11 (quoting Denning, 560).) Yanagimachi, another post-filing date reference, is cited for teaching that "[c]loning efficiency—as determined by the proportion of live offspring developed from all oocytes that received donor cell nuclei—is low regardless of the cell

type (including, embryonic stem cells) and animal species used," which the reference attributes to "faulty epigenetic reprogramming of donor cell nuclei after transfer into recipient oocytes. Cloned embryos with major epigenetic errors die before or soon after implantation." (Answer 11-12 (quoting Yanagimachi, Abstract).)

The Examiner asserts as "to targeting the second allele of a heterozygous gene *in vitro*, the skilled artisans have shown repeatedly that this had been extremely difficult to accomplish." (Answer 14.) The Examiner cites Phelps, which describes making pigs that are homozygous for α1,3GT inactivation (*id.*). According to the Examiner, while Phelps intended to knockout the second α1,3GT allele, that is not in fact what occurred (Answer 14 (citing Phelps, 413)). Phelps in fact employed a new method for selecting α1,3GT-double negative cells, which allowed them to select for cells that had a knockout of the second α1,3GT allele by mechanisms other than targeted homologous recombination (Answer 14-15 (citing Phelps 413)). The Examiner thus asserts that Phelps "confirms the difficulty of double knockout [of] a gene in a somatic cell, which has not been resolved using routine experimentation even long after instant priority date." (Answer 15.)

The Examiner also relies on Kuroiwa, who discloses that "[g]ene targeting in somatic cells versus embryonic cells is a challenge; consequently there are few reported successes and none include the targeting of transcriptionally silent genes or double targeting to produce homozygotes." (Answer 15 (quoting Kuroiwa, Abstract)). In addition, Kuroiwa is also cited for teaching that breeding to homozygosity is limited in species that have a long generation interval, such as a sheep, and are

negatively impacted by the consequences of inbreeding (Answer 15 (citing Kuroiwa, 775)). As to the production of animals that are homozygous for the knockout of the α1,3GT gene, Kuroiwa, the Examiner states, acknowledges the success of Phelps, but points out that the method is not widely applicable (Answer 16 (citing Kuroiwa, 775)). Kuroiwa's success, the Examiner notes, "was brought about by another innovative approach, i.e. sequential application of gene targeting by homologous recombination and rejuvenation of cell lines by cloned fetuses. Such approach was developed long after the instant filing date, and the specification fails to teach such a method, thus, the reference does not support the enablement of instant claimed invention." (Answer 16.)

The relative skill of those in the art, the predictability or unpredictability of the art, and the quantity of experimentation necessary:

Even though the level of skill in the art is high (the ordinary artisan having a Ph.D), the Examiner asserts that "in light of the state of the art and the levels of the skilled, the lack of survival to term in appellant's αl,3GT+/- ovine fetuses is less likely an accident, but reflects real challenges attributed to faulty epigenetic reprogramming and major genetic dysregulation." (Answer 12.)

As to targeting of the second allele of a heterozygous gene, the Examiner asserts that the Specification : "fails to teach how to overcome the difficulties taught by Denning," and "fails to teach the innovative methods" of Phelps and Kuroiwa, thus the success achieved by those post-fling date references does not support the enablement of the instant Specification and claims (*id.* at 16). According to the Examiner, the Specification "fails to teach how to overcome the art known hurdles in knocking out the second

allele of a ovine cell in culture, it fails to teach the innovative methods found in the post-filing art, and thus it fails to provide an enabling disclosure for instantly claimed invention." (*Id.*)

The Examiner thus concludes that "it requires further development of the art (undue experimentation) to provide a homozygous knockout ovine cell." (*Id.* at 14.)

Appellants argue that there is no legal requirement that a working example be provided in the Specification, and that the claims are fully enabled "because the only elements missing from the working examples can be achieved as a matter of routine experimentation by the skilled reader." (Br. 7.)

We agree that the presence or absence of a working Example is not dispositive on the issue of enablement. That was acknowledged by the Examiner (Answer 12 (citing MPEP § 2164.02-2164.03)). The Examiner concluded that enablement was lacking based on the state of the art, the level of skill in the art, the guidance presented by the Specification, as well as the lack of live heterozygous ovine animals (Answer 13). We do note, however, that the lack of working examples is evidence that the claims on appeal are not enabled. *See Application of Colianni,* 561 F.2d 220, 222 (CCPA 1977) (upholding claim rejection and considering the lack of a working example as evidence that claims were not enabled). In addition, we agree with the Examiner that the evidence of record establishes (see the analysis of the Examiner and the analysis below) that the claimed invention cannot be achieved by routine experimentation, and the rejection is affirmed.

The Specification, Appellants assert, discloses the nucleotide sequence for sheep α1,3GT, and Example 3 demonstrates how the sequence

may be used to create targeting vectors, which may then be used to inactivate the α1,3GT gene in isolated fibroblasts from different strains (Br. 7). Heterozygous sheep were created using the targeted cells, according to Appellants, as shown in Example 6 of the Specification, using standard techniques in the field of animal cloning (*id.*). Homozygous knockout animals can then be created by using a double knockout cell in the cloning process or by cross-breeding heterozygous animals (*id.* at 8). According to Appellants, the use of nuclear transfer technology in cloning animals "is proven technology that created Dolly the sheep. The nuclear transfer method has been fully described and enabled in issued U.S. patents 6,147,276 and 6,252,133 (Campbell & Wilmut, Roslin Institute)." (*Id.* at 11.)

Appellants cite a number of references to support their assertion that "cloned animals may readily be made from genetically altered cells according to the Campbell & Wilmut method." (*Id.* at 12.)

Uchida et al. ("Production of transgenic miniature pigs by pronuclear microinjection," 10 *Transgenic Research* 577-580 (2001)) describes production of transgenic pigs using the Huntington gene. The article does not describe the production by cloning of a double knockout of an active gene as required by the instant claims. Moreover, as noted by the Examiner, Uchida stated post-filing date (2001) that this was the first successful report concerning the production of a transgenic miniature pig by pronuclear injection, suggesting that the production of transgenic animals was not routine as of the effective filing date of the instant invention, May 15, 2000.

Bondoli et al. ("Cloned Pigs Generated From Cultured Skin Fibroblasts Derived from a H-Transferase Transgenic Boar," 60 *Molec.*

Repro. Dev. 189-195 (2001)) reports cloned pigs generated from skin fibroblasts derived from a boar with an H-transferase gene. Again, this reference is not drawn to the production by cloning of a double knockout of an active gene as required by the instant claims.

Lai et al. ("Transgenic Pig Expressing the Enhanced Green Fluorescent Protein Produced by Nuclear Transfer Using Colchicine-Treated Fibroblasts as Donor Cells," 62 *Molec Repro. Dev.* 300-306 (2002)) discloses the production of a transgenic pig expressing a green fluorescence protein. Lai, as noted by the Examiner, is again drawn to a transgenic pig, not to a double knockout ovine (Answer 28).

McCreath et al. ("Production of gene-targeted sheep by nuclear transfer from cultured somatic cells," 405 *Nature*, vol. 405 1066-1069 (July 2000)) describe "gene targeting in fetal fibroblasts to place a therapeutic transgene at the ovine α1(I)procollagen (COL1A1) locus and the production of live sheep by nuclear transfer." McCreath is thus drawn to the production of a transgenic ovine, and not a double knockout of an active gene.

Lai et al. ("Production of α-1,3-Galactosyltransferase Knockout Pigs by Nuclear Transfer cloning," 295 *Science* 1089-1092 (February 2002)) report the production of four live pigs in which one allele of the α-1,3-galactosyltransferase has been knocked out. Lai was published approximately two years after the effective filing date of the instant application, and does not report the production of double knockout pigs. In addition, Lai notes that "[a]ttempts at targeting the GGTA locus in pigs [referencing Bondoli] and sheep [referencing Denning] have also been reported, but these failed to result in live birth of animals with the desired

modification. In both cases, difficulties in obtaining viable targeted donor cell clones were encountered." (Lai, p. 1090. first column.)

Dai et al. ("Targeted disruption of the α1,3-galactosyltransferase gene in cloned pigs," 20 *Nature Biotech.* 251-255 (March 2002)) report the disruption of one allele of the pig α1,3 gene in male and female porcine primary fibroblasts. Dai thus reports a knockout pig that is heterozygous for α(1,3)GT gene, not homozygous knockout sheep.

Denning et al. ("Deletion of the α1,3-galactosyltransferase (GGTA1) gene and the prion protein (PrP) gene in sheep," 19 *Nature Biotech.* 559-562 (June 2001))[6] describes deletion of vital regions from the α1,3-galactosyltransferase gene and from the prior protein gene (Denning, Abstract). Eight pregnancies were carried to term, with four live births from the prion protein line (*Id.* at 560, column 2.). Three lambs died soon after birth, and the last lamb was euthanized after 12 days after developing dyspenea due to pulmonary hypertension and right-sided heart failure, which the reference states are common abnormalities in cloned sheep (*id.*).

Denning notes that the "high incidence or mortality reported here may indicate that genetic modifications or prolonged culture is detrimental to development," concluding that "prolonged culture, in combination with the stringent selection required for somatic gene targeting, may produce cell lines that are less competent at producing viable clones." (*Id.*) Moreover, the fact that the live births were from the prior protein line may indicate "that cloning efficiency differs between cloned sheep having different target

[6] Denning, as noted by the Examiner, describes the instant invention post-filing date (Answer 28).

genes and the targeting gene might be relevant to the success of reproductive cloning" (Answer 28-29.)

Finally, Denning discloses that:

> The death of the targeted fetuses and lambs emphasizes the need to improve the efficiency of the technology. Once this is achieved, effective ablation of gene function will usually require both alleles to be disrupted. Given the limited proliferative capacity of cells currently used in nuclear transfer, achieving this from a single clonal population will be difficult. Alternatively, conventional breeding could be used with animals surviving to reproductive maturity. However, this would take a minimum of 18 months in sheep, even if the modification were introduced simultaneously into male and females and the cloned animals interbred. A different approach would be to clone by nuclear transfer from the cells in which the first allele has been targeted, re-isolate cell lines from the cloned fetal material, and then target the second locus in these cells. Ultimately, however, the fastest route to multiple genetic changes would be to extend the window to achieve targeting, either by increasing the overall efficiency of targeting or by using cells with an extended life span that still retain their totipotency for nuclear transfer.

(Denning, 561, second column.)

Thus, Denning notes that further work is needed in order to obtain successful clones, demonstrating that it was not just a matter of routine experimentation to achieve an ovine that homozygous for inactivation of an α1,3GT gene.

Schnieke et al. ("Human Factor IX Transgenic Sheep Produced by Transfer of Nuclei from Transfected Fetal Fibroblasts," 278 *Science* 2130-2133 (December 1997)) reports the production of human factor IX transgenic sheep, wherein ovine fibroblasts were transfected with human factor IX gene and used as donors for nuclear transfer to enucleated oocytes.

Schneike is thus not drawn to the production of a double knockout ovine using nuclear transfer. We do note that Schneike, one of the few pre-filing date references cited by Appellants, does teach that "[o]ur approach has shown that cell-mediated transgenics is possible in a mammal other than the mouse. The technique is still in the early stages of development and problems remain to be addressed—in particular, the lack of spontaneous parturition and the incidence of perinatal mortality." (Scheike, 2132, middle column.) Thus, Schneike did not consider the use of nuclear transfer in the production of transgenic animals to be routine.

Cibelli et al. ("Cloned transgenic Claves Produced from Nonquiescent Fetal Fibroblastsm" 280 *Science* 1256-1258 (May 1998)) transfected bovine fibroblasts with a marker gene, which was then fused to nucleated mature oocytes. Again, Cibelli is drawn to transgenic calves and is not drawn to the production of a double knockout ovine using nuclear transfer.

Kuroiwa et al. ("Sequential targeting of the genes encoding immunoglobulin-μ and prion protein in cattle," 36 *Nature Genetics* 775-780, (July 2004)) is cited for teaching the production of cattle that are homozygous for inactivation of the bovine gene encoding IgM μ-chain (IGHM) (Br. 13). According to Appellants:

> Cells were targeted on one allele and used as donors to make heterozygous fetuses. Tissue was harvested, retargeted using *non-isogenic* vectors, and used to make homozygous knockout animals. *Five rounds* of harvesting fetal tissue, genetic modification, and nuclear transfer, produced tissue with this genotype: homozygous inactivation of IGHM, containing a *Cre* transgene, and homozygous inaction of the PRNP gene (responsible for mad cow disease). Nine pregnancies having the five modifications have survived beyond 60 days.

(Br. 13.)

Kuroiwa, a postfiling date reference, also does not support the enablement of the instant claims as of their filing date. Kuroiwa, which was published in July 2004, approximately four years after Appellants claimed priority date of May 15, 2000, as noted by the Examiner in the statement of the rejection, teaches that "[g]ene targeting in somatic cells versus embryonic stem cells is a challenge, consequently there are few reported successes and none include the targeting of transcriptionally silent genes or double targeting to produce homozygotes." (Kuroiwa, Abstract.) Kuroiwa in fact develops a method of rapid gene targeting in cattle consisting of sequential application of gene targeting by homologous recombination and rejuvenation of cell lines by production of cloned fetuses (Kuroiwa, 775, second column). Thus, while Kuroiwa may employ to a certain extent the the basic Campbell & Wilmut method, in order to obtain the double knockout cattle, it had to develop further methods, methods which are not described in the instant Specification.

Ramsoondar et al. ("Production of α1,3-Galactosyltransferase-Knockout Cloned Pigs Expressing Human α1,2-Fucosyltransferase," 69 *Biol. Reprod.* 437- 445(2003)) report the production of α1,3-GT knockout, HT-transgenic pigs. Promoter-trap targeting constructs consisting of mainly intron sequence and a Kozak consensus sequence to initiate translation were used to target the genes (Ramsoondar, 438, first column). In addition, Ramsoondar developed two efficient PCR strategies to detect targeted clones (*id.*). At the time of publication, only pigs heterozygous for the α1,3gene were achieved, although the generation of homozygous α1,3(GT knockout pigs was underway (*id.* at Abstract).

Thus, Ramsoondar used a specific construct targeting a specific region of the pig α(1,3)GT gene. The method that led to the production of pigs that were heterozygous for the α1,3GT gene is not taught by the instant Specification, and thus Ramsoondar does not support Appellants' assertion that the disclosure as filed enables the claims on appeal.

Sendai et al. ("Heterozygous Disruption of the α1,3-Galactosyltransferase Gene in Cattle," 76 *Transplantation* 900-902 (September 2003)) report the first successful production of heterozygous α1,3GT cattle. Sendai was published approximately three years after the effective filing date of the instant application, and does not report the production of double knockout cattle.

"Enablement . . . is determined as of the application filing date. *In re Brana*, 51 F.3d 1560, 1567, n.19, 34 USPQ2d 1436, 1442 n. 19 (Fed. Cir, 1995). While it is true that post-filing evidence may be relied upon for certain purposes, *see Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987):

> [A] later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling . . . . [A later publication may be used] as evidence that the disclosed device would have been operative. *Compare In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977) ("This court has approved use of later publications as evience of the state of the art *existing on the filing date* of an application." (footnotes omitted) (emphasis in original)) *with In re Glass*, 492 F.2d 1228, 1232, 181 USPQ31, 34 (CCPA 1974) (later publications which add to the knowledge of the art cannot be used to supplemement an insufficient disclosure).

As the *Glass* court noted, "[i]t is an applicant's obligation to supply enabling disclosure without reliance on what others *may* publish after he has

filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in the position to file." *Glass*, 492, F.2d at 1232, 181 USPQ at 34 (emphasis in original).

We agree with the Examiner that the above references do not support that the claims were enabled as of the filing date, but in fact support the Examiner's finding that it would require an undue amount of experimentation to produce an ovine animal that is homozygous for inactivation of an α1,3GT gene, and thus it would require an undue amount of experimentation to practice the claimed invention. The above references, especially Denning, Kuriowa, and Ramsoondar, establish that methods beyond the basic the Campbell & Wilmut method of cloning relied upon by the Specification, are required to produce an animal that is a double knockout for the α1,3GT gene. Appellants have not provided evidence as to why the disclosures of those post-filing date references, as well as the other post-filing date references relied upon, were available to those skilled in the art as of the effective filing date of May 15, 2000. Therefore, the Specification does not enable the production of an ovine that is homozygous for inactivation of an α1,3GT gene without an undue amount of experimentation.

As noted by the Examiner:

> [I]t has become apparent that appellant has constantly rel[ied] on post-filing date references as support for enablement of the instant claimed invention. In the instant case, appellant heavily relie[s] on α(1,3)GT null pigs that bec[a]me available four years after the instant filing date for enablement of the claimed invention on sheep. However, none of the post-filing success in α(1,3)GT null pigs could be achieved in the absence of further advance in knowledge and technology of animal cloning that become available after instant filing date. Thus,

> judged as of the filing date, the instant disclosure is insufficient to provide enablement for what is claimed.

(Answer 30.)

Appellants assert that as the cited references, especially Lai (*Science*, 2000), Dai, Denning, Ramsooder, Sendai and Kuroiwa demonstrate that animal cloning techniques are in wide-spread use (Br. 14-15), and thus "the only relevant question in relation to the invention claimed in this application is *whether knocking out both α1,3GT alleles would somehow compromise the viability of the animal.*" (*Id.* at 15 (emphasis in original).) Appellants argue that cannot be the case as "[h]umans and other Catarrhine primates are exceptions amongst mammalian species as not having an expressed αl,3GT gene. We seem to get along quite well without it. The α1,3GT gene has been obtained from two other species that normally express it, and used to create homozygous knockouts without difficulty." (*Id.* (citing d'Apice (US Patent No. 5,849,991, issued December 15, 1998), Phelps et al. ("Production of α1,3-Galactosyl-transferase Deficient Pigs," 299 *Science* 411-414 (2003)) and Kolber-Simonds et al. ("Production of α1,3-Galactosyltransferase null pigs by means of nuclear transfer with fibroblasts bearing loss of heterozygosity mutations," 101 *PNAS USA* 7335-7340 (May 2004))).

We do not disagree with Appellants that knocking out both αl,3GT alleles should not affect the viability of the animal. The rejection as set forth in the Answer, however, is not whether producing a double knockout of the αl,3GT would, in and of itself, affect the viability of the animal, but whether it would require an undue amount of experimentation to produce an ovine that is homozygous for inactivation of an α1,3GT gene. We conclude, for the reasons set forth above, that it would require an undue amount of

experimentation to produce such an animal. Thus, we disagree with Appellants statement that Lai (*Science*, 2000), Dai, Denning, Ramsooder, Sendai and Kuroiwa demonstrate that animal cloning techniques are in wide-spread use, as the references do not support Appellants' assertion that the Specification is enabling for the production of an ovine that is homozygous for inactivation of an α1,3GT gene.

Appellants argue that the knockout pigs of Phelps were made in accordance with the methods disclosed in the instant Specification (Br. 16). According to Appellants:

> First, the pig α1,3GT gene was used to make heterozygous knockout donor cells, which were then used to clone heterozygous knockout pig (page 412, col. 1; described in the present application *inter alia* on page 38, line 5 to page 40, line 19; and page 41, line 22 to page 42, line 5). Next, homozygous knockout cells were made by a targeting the other allele in the donor cells using a knockout vector, and selecting cells deficient in the Galα (l,3)Gal surface antigen (page 412, col. 1; described in the present application *inter alia* on page 41, lines 9-13 and 17-20; and page 42, lines 6-16). Finally, double knockout cells were used as donor cells for nuclear transfer to produce homozygous knockout animals (abstract; described in the present application *inter alia* on page 38, line 9 to page 40, line 19).
>
> Four double-targeted female piglets were produced by Phelps et al., of which three had α1,3GT inactivated on both alleles (page 412, col. 3 ff).

(*Id.*)

Phelps, however, did not achieve a pig that was a double knock-out for the α1,3GT gene using the methods set forth in the Specification. Rather, Phelps reports:

> Although our intent was to knock out the second allele of the α1,3GT gene by homologous recombination, *this did not occur*. Instead, because we used this powerful selection method, which allows us to isolate any event that results in loss of α1,3GT activity, we discovered a mutation in the second allele of the α1,3GT gene. Had we used standard selection methods with puromycin or hygromycin, we would not have found the mutation.

(Phelps, 413, last column (emphasis added).)

Similarly, Appellants assert, the knockout pigs of Kolber-Simonds et al. ("Production of α 1,3-galactosyltransferase null pigs by means of nuclear transfer with fibroblasts bearing loss of heterozygosity mutations," *PNAS*, Vol. 101, pp. 7335-7340 (2004)) were made by knocking out the two α1,3GT alleles in two sequential rounds of cloning. Cell lines established from heterozygous knockout cells were selected for spontaneous inactivation of the second allele using antibody staining. They were then used successfully as nuclear donors: 48 transfers resulted in 17 pregnancies, and 4 homozygous α l,3GT knockout piglets." (Br. 16.)

Again, the double knockout pigs of Kolber-Simmonds were achieved by spontaneous loss of the wild type (WT) allele (Kolber-Simonds, p. 7335, first column). According to the reference, "the nature and frequency of spontaneous second allele mutations seems to be greatly influenced by the inbred genetic background." (*Id.* at 7339, sentence bridging columns 1 and 2.) Thus, the double knockout pigs produced by Kolber-Simonds were also not achieved using the methods disclosed in the instant Specification.

Appellants argue that the Examiner has relied on the lack of working Examples in asserting the art of making knockout animals is unpredictable, but has not raised any specific technical issue as to "why the making of a

knockout sheep should pose special technical difficulties—difficulties that were not experienced in making αl,3GT knockouts in two other animal species." (Br. 8.) With respect to Denning, cited by the Examiner in the Office Action, Appellants assert that it was only a "preliminary report" and "does not support the contention that gene targeting in sheep is an uncertain process." (*Id.* at 19.)

According to Appellants, the article demonstrates that sheep cells can be correctly targeted for inactivation of the αl,3GT gene (*id.* (citing Figure 2)). The targeted cells may then be successfully used for nuclear transfer, as the αl,3GT knockout gave rise to a viable embryo; the PRP knockout gave rise to 3 live births; and viable animals have been produced that targeted the COL1A1 locus (discussing reference 5 of the article) (*id.*). Finally, Appellants assert, the article demonstrates, as can be seen from the data in Table 2, that knocking out the αl,3GT gene does not decrease the viability of the embryo (*id.*). The authors of that article, Appellants argue, lost their funding, and that is the reason that knockout sheep were not ultimately produced.

Appellants conclude:

> There is no question that large animal cloning is a costly and time-consuming process, whether or not *the nuclear donor cell has any kind of genetic alteration.* But that does not mean that the claimed invention is in any way inadequately described or enabled. The cloning step required to complete the invention claimed in this application, while costly, is entirely straight forward. *It can be accomplished without undue experimentation,* well within the Wands standard. There is nothing missing from the specification that the skilled reader needs in order to put this invention into practice.

(*Id.* at 20 (emphasis in original).)

Appellants position, however, that the cloning step required to complete the invention claimed in this application, while costly, is entirely straight forward, is not supported by a preponderance of the evidence, as discussed above. As noted above, Denning states that the high mortality rate "emphasizes the need to improve the efficiency of the technology," and that "[g]iven the limited proliferative capacity of cells currently used in nuclear transfer, achieving this from a single clonal population will be difficult." (Denning, 561, second column.) Thus, Denning supports that additional advances in the art are needed, supporting the Examiner's position that it would require an undue amount of experimentation to practice the claimed invention.

Appellants also rely on the Declaration of Ian Wilmut, filed under 37 C.F.R. § 1.132 on September 23, 2004, to support their position that the claimed invention is enabled by the Specification as filed (Br. 20). According Appellants,

> Dr. Wilmut explains that genetically modified animals can readily be made by the methods described in U.S. patents describing nuclear transfer, and provides a number of illustrations. He also explains that the early death of α(1,3)galactosyltransferase knockout sheep fetuses reported in the Denning article is often observed in cloned animals, and not attributable to an effect from the α1,3GT gene. He explains that the sheep αl,3GT gene provided in this application can be used to make αl,3GT knockout sheep, just as the pig α1,3GT gene has been used to make αl,3GT knockout pigs.
>
> Thus, even if it takes several attempts to obtain a working example because of a low frequency of successful cloning events, there is no undue experimentation involved. The skilled reader simply repeats the procedure until a α1,3GT knockout sheep is obtained.

(*Id.* at 20-21.)

While we acknowledge that declaratory evidence as to issues of fact is entitled to substantial weight, *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996), "[a]n expert opinion is no better than the soundness of the reasons supporting it." *Perreira v. Secretary of the Dept. of HHS*, 33 F.3d 1375, 1377 (Fed. Cir. 1994). We find that the Examiner did a thorough analysis of the arguments and evidence presented in the Declaration. We thus agree with the Examiner that the Declaration is not sufficient to rebut the findings underlying the conclusion that the Specification fails to enable the claimed subject matter for the reasons the Examiner set forth (Answer 32-36).

Therefore, after considering the *Wands* factors and weighing the evidence of record, we conclude that a preponderance of the evidence supports the conclusion of the Examiner that the claims contain subject matter that was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427, 7 USPQ2d 1152, 1156 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office); *In re Kollar*, 286 F.3d 1326, 1329, 62 USPQ2d 1425, 1427 (Fed. Cir. 2002) ("The PTO bears the initial burden of demonstrating that the preponderance of the evidence establishes *prima facie*, facts supporting the conclusion that the claimed invention was on sale within the meaning of § 102(b)."). The rejection of claims 1-6, 13-16, and 33-37 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, is thus affirmed.

Appellants argue as to the homozygous knockout cells of claims 4 and 33-37, that the cells can be created in culture, without doing any animal cloning at all (Br. 8). According to Appellants, an "extensive description of how to make α 1,3GT homozygous knockout cells in culture is provided in the specification beginning on page 40, line 20." (*Id.* at 10 and 21.)

The only method of using the cells, however, disclosed by the Specification, is in the generation of an ovine animal that is homozygous for inactivation of an α1,3GT gene. For Example, the Specification teaches at page 11 that "mammalian cells that have had an α 1,3GT gene inactivated artificially in at least one haplotype are used to produce animals that do not express the Gal α (1,3)Gal epitope." 35 U.S.C. § 112, first paragraph, requires the Specification to teach the skilled artisan to make and/or use the invention. Because the Specification is not enabling for the production of an ovine animal that is homozygous for inactivation of an α1,3GT gene, it does not enable the skilled artisan to use the knockout cells of claims 4 and 33-37. As noted by the Examiner, "the lack of enablement issue here is . . . whether one can obtain the homozygous knockout animals without undue experimentation." (Answer 31.)

As to claim 5, Appellants argues that claim 5 "depends from claim 4, and requires only that the process for making the cell involve at least one nuclear transfer event. This may involve the making of a cloned animal, or just the making of a single cell or cell culture by nuclear transfer." (Br. 22.) This rejection is also affirmed for the reasons set forth above with respect to the rejection of claims 4 and 33-37.

As to claim 13, Appellants argue that claim 13 "depends from claim 4, and covers the use of heterozygous or homozygous α 1,3GT knockout cells

for making homozygous α1,3GT knockout sheep." (Br. 22.) As set forth above, however, the Specification does not enable the skilled artisan to produce a homozygous α1,3GT knockout sheep, and the rejection is affirmed for the reasons set forth above.

As to claims 1-3, Appellants argue that claim 3 "covers a cell or tissue that does not express α1,3GT. Claims 1 and 2 cover tissue devoid of the Galα(1,3)Gal epitope. Again, cells having these properties can be harvested from a α1,3GT knockout animal, or produced in *vitro* by genetic manipulation of cultured cells." (Br. 22.) This rejection is also affirmed for the reasons set forth above with respect to the rejection of claims 4 and 33-37.

As to claim 16, Appellants argue that claim 16 "depends from claim 1, calling out a particular use of the cells of claim 1 for transplanting into a mammal having circulating antibody against Galα(1,3)Gal determinants - e.g., a non-cattharine primate, or a α1,3GT knockout mouse or pig." (Br. 22.) Appellants also present arguments as to why claim 16 is enabled for a method of xenotransplantation (Br. 23-24). But as the Specification is not enabling for a method of making an ovine homozygous for inactivation of an α1,3GT gene, it is not enabling for the xenotransplantation method of claim 16 as the Specification does enable the production of the tissue required for the xenotransplanation. Thus, the rejection of claim 16 is affirmed for the reasons set forth above.

CONCLUSION

In summary, we reverse the rejection of claims 5 and 6 under 35 U.S.C. § 101 as not supported by a substantial utility, a well-established utility. The rejection of claims 1-6, 13-16, and 33-37, however, under 35

U.S.C. § 112, first paragraph, as failing to be supported by an enabling disclosure, is affirmed. Thus, as a rejection as to all of the claims on appeal has been affirmed, the Examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc

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